

Repurposing a Blood Cancer Treatment to Treat Muscle Contractures in Cerebral Palsy Patients



NORTHWESTERN UNIVERSITY



Richard L. Lieber, Ph.D.
Chief Scientific Officer
Skeletal Muscle Research



Andre Domenighetti, Ph.D.
Research Scientist
Muscle Epigenetics



Masha Kocherginsky, Ph.D.
Professor
Biostatistician



John Cunningham, M.D.
Chair and Professor
Pediatric Oncology

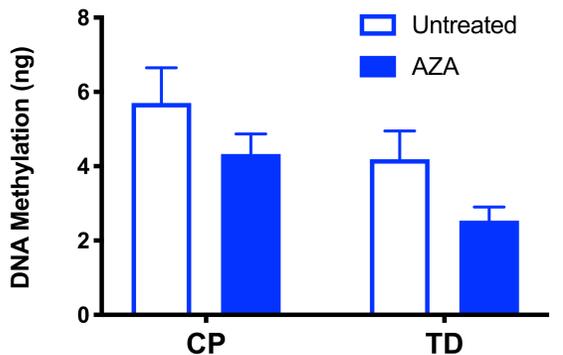
PROPOSED TREATMENT

Repurposing the FDA-approved DNA hypomethylating agent 5-azacytidine (AZA), used to treat blood cancer, to restore muscle function in patients with CP.

Muscle stem cells are required for growth, and muscles do not appear to grow in CP patients. CP patients have fewer muscle stem cells, and these stem cells are characterized by increased DNA methylation when compared to cells from typically developing (TD) children. Previous research has shown that AZA can restore the biological function of muscle stem cells from CP patients in vitro, as well as reduce DNA methylation.

While AZA has been used for more than 30 years to treat pediatric blood cancer, it has never been explored as a potential treatment for muscle contractures. AZA may present a new, inexpensive, and effective nonsurgical treatment for muscle contractures in patients with CP.

This approach may also be applied to other types of contractures that result from stroke, spinal cord injury, or head injury.



Data from Domenighetti et al. 2018. AJP 315:C247

SUMMARY STATEMENT

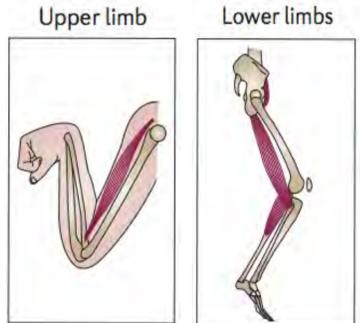
A clinical trial of 30 pediatric patients with cerebral palsy (CP) to determine the optimal treatment protocol utilizing 5-azacytidine (AZA), an FDA-approved blood cancer treatment, to treat muscle contractures

DISEASE/CONDITION

Cerebral palsy (CP) is the most common cause of childhood motor disability, affecting approximately 1 in 600 infants, with approximately 17 million affected people worldwide. Muscle contractures affect about one-third of CP children and cause loss of movement, decreased strength, and pain.

The resulting loss in mobility presents many challenges for these children and families, including:

- Severe limitations in access to school
- Low self-esteem, feelings of isolation and loneliness, and depression



CURRENT TREATMENT

Current treatment methods for muscle contractures are limited:

- Splinting/casting/orthotics
- Exercise therapy & stretching
- Anti-spasticity medications
- Surgery (only available in highly developed and wealthy regions)

While these treatments may slightly reduce disability, they do not prevent or resolve the underlying biological impairment in CP patients.

PROJECT

The proposed dose-escalation study will establish the dose of AZA that is safe and effective in treating muscle contractures in children with CP.

The trial will enroll 30 patients with cerebral palsy who have already consented for surgery due to muscle contracture. 15 patients will receive AZA prior to surgery and 15 will receive standard-of-care treatment. Muscle biopsies will be taken during surgery, followed by blood draws at 15, 21, and 28 days after surgery.



Specific Aims

- Determine the level of acceptance by patients and their families to an injection prior to surgery
- Establish the optimal dose to demethylate and restore function to human muscle stem cells
- Determine whether the demethylation results in any measurable change in muscle contracture

This study could establish a new paradigm for nonsurgical treatment of muscle contracture by “biologically enabling” muscles with AZA treatment. If positive data are seen, future plans include applying for follow-on funding to test the effect of AZA in combination with other modalities (e.g., stim, exercise) to potentiate AZA’s effects.



CUREACCELERATOR[®] *Live!* for Chicago

September 15, 2020

